

In re Application of:  
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Filed: September 15, 1999  
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### REMARKS

After entry of the present amendment, claims 22, 23, 33, and 35-41 will be pending and under consideration. The amendments submitted herewith are supported by the specification and original claims and do not add new matter. The amendments do not require a new search or raise new issues for consideration because they merely address issues already raised by the Examiner or define Applicant's invention more clearly. It is submitted that the amendments place the claims in condition for allowance or in better condition for appeal by reducing the number of issues for consideration on appeal. The amendments were not made earlier in the prosecution because it is maintained that the previously pending claims were allowable. Since the amendments do not add new matter or require a new search or consideration, and place the claims in condition for allowance or in better condition for appeal, entry of the amendments is respectfully requested. Additionally, applicant respectfully requests reconsideration of the present application in view of the amendments and the discussion herein.

In the present communication, claims 1-10, 16-21, 24-32, and 34 have been cancelled without prejudice, claims 22, 23, 33, and 36-38 have been amended, and claims 39-41 have been added. A marked up copy to show changes made is attached herewith as Exhibit A.

No new matter is added by the present amendments and added claims. For example, the amendments to claims 22 and 23 change dependency to independent claim 33 from canceled claim 10. The amendment to claim 33 is supported by page 32, lines 16-18, which indicates that the nucleic acid of interest whose methylation state can be assayed by a method of the present invention includes MINT31. Page 25, lines 15 -16 indicates that MINT31 corresponds to regions 1 and 2 of the CACNA1G CpG island. Furthermore, the amendment to claim 33 is supported by the specification as filed at pages 24-27 which illustrate that one or both of the first region and the second region are methylated in many different cancers. More particularly, for example, the amendment to claim 33 is supported by page 25, lines 1-2, which indicate that regions 1 and 2 were frequently methylated in cancer. Finally, page 25, lines 2-3 teaches that

regions 1 and 2 are methylated in most cancers other than gliomas. The amendment to claim 36 cancels primer pairs that are not directed at the first or second region of the CACNA1G CpG island. The amendments to claims 37 and 38 delete the term "cellular proliferative disorder" from these claims to conform to the amendment of claim 33 in which this term was deleted. Claim 38 deletes astrocytoma and glioblastoma, types of gliomas. Newly added claims 39 and 40 are supported by page 27, lines 2-5. Newly added claim 41 is supported for example by page 25, lines 21 to 26, which indicates that methylation of CACNA1G in cancer can include methylation of the first and the second regions of the CpG island of CACNA1G, in combination with methylation of the other recited regions of the CpG island (Page 25, lines 4-7).

**Rejection Under 35 U.S.C. § 112, Enablement**

Claims 10, 16-24, and 33-38 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being disclosed in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicant respectfully traverses the rejection. The Office Action reiterated verbatim the allegation of the previous Office Action that the present invention is not enabled because the claimed invention is overly broad in being directed to identifying any cellular proliferative disorder, and to any CpG island within the recited genes. Furthermore, the Office Action repeated verbatim its assertion that it is unpredictable which CpG islands, and which subregions within those islands, are associated with various tissues based on cited published reports, for example related to acute myelogenous leukemia (AML) (Toyota et al., Blood, Vol. 97, 2823 (2001)), and results of the present specification, which indicate that the hypermethylated gene CACNA1G, is not hypermethylated in all cell proliferative disorders. Finally, the Office Action reasserted its allegation that the present invention is not enabled because experimental details are not presented regarding the correlation of hypermethylation and cellular proliferative disorders for all of the recited genes, except CACNA1G.

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In response to the Applicant's arguments in the Response filed August 15, 2002, the Office Action cites Moinova et al. (*PNAS*, 99:4562, 2002) to allegedly establish that genes that are hypermethylated in certain cancers are not hypermethylated in all cancers, as allegedly exemplified by hypermethylation of the *HLTF* gene in primary colon cancer, but not breast or lung cancer. Furthermore, the Office Action cites Kazuhiro et al. (*Clin. Cancer Research*, 8: 3164) in allegedly teaching that *MLH1*, *HRK* and *CACNA1G* are not methylated in oral squamous cell carcinomas. As a preliminary matter, "Kazuhiro et al." cited in the Office Action should have been cited as Ogi et. al. (*Clin. Cancer Research*, 8, 3164 (2002)).

Applicant respectfully submits that the pending claims are enabled by the disclosure as filed. Specifically, with respect to claim 33, the Office Action alleges that it is unpredictable which cellular proliferative disorders are associated with hypermethylation and which CpG subregions are associated with cancers, and reiterates the allegation that the results of Ogi et al. support that *CACNA1G* CpG island is not methylated in oral squamous cell carcinoma. However, a close comparison of Ogi et al. with the pending application further establishes that the CpG island of *CACNA1* as defined in the present specification is hypermethylated in the vast majority of cancers. Ogi et al. analyze methylation of 12 loci in squamous cell carcinomas, including *CACNA1G* and *MINT31*. Although they report that *CACNA1G* did not exhibit aberrant methylation, they report that *MINT31* exhibited aberrant methylation. The present invention indicates that the *CACNA1G* CpG island is divided into 8 regions. Regions 1 and 2 of the *CACNA1G* CpG island according to the pending specification correspond to *MINT31* (Page 25, lines 15-16). Therefore, what Ogi et al. report as methylation of *MINT31* corresponds to hypermethylation of regions 1 and 2 of *CACNA1G*. Accordingly, the results reported in Ogi et al. establish that regions 1 and 2 of the *CACNA1G* CpG island are hypermethylated in oral squamous cell carcinoma, thereby further supporting the conclusion of the present specification

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that regions 1 and 2 of the CACNA1G CpG island are hypermethylated in a wide variety of cancers and cancer cell lines.

As indicated in the present specification, regions 1 and 2 (MINT31) were frequently methylated in cancer cell lines. The present specification gives details regarding the specific patterns of methylation within the CpG region of CACNA1G. The specific patterns observed illustrate that methylation of regions 1 and 2 (island 1) is frequent in cancers since methylation of these regions is included in all of the methylation patterns of the CACNA1G methylation. Furthermore, the present specification teaches that regions 1 and 2 of the CACNA1G CpG region are much more frequently methylated in cancers compared to the CpG island just upstream of CACNA1G (Page 27, lines 28-29).

Regarding claim 33, the Office Action further alleges that not all subregions of CACNA1G are hypermethylated in all cancers, for example gliomas. However, the Office Action acknowledges that it is not necessary to demonstrate that the CACNA1G CpG island is hypermethylated in every cellular proliferative disorder to enable claim 33. Furthermore, claim 33 as amended clarifies that the claimed method is not directed at detecting gliomas. Additionally, the present specification discloses that regions 1 and 2 (MINT31) of the CACNA1G CpG island are hypermethylated in a wide variety of cancers. The specification at page 24, line 11 to page 25, line 3 discloses that regions 1 and 2 of the CACNA1G CpG island are hypermethylated in primary cells and cell lines from colon cancer, lung cancer, hematopoietic cancer, prostate cancer, and breast cancer. Furthermore, the specification discloses that the CpG region of CACNA1G is aberrantly methylated in primary tumors from colorectal cancer, colorectal adenoma, gastric cancer, and acute myelogenous leukemia (page 26, line 28 to page 27, line 4).

Furthermore, reports published after the priority date of the pending specification, further establish that regions 1 and 2 (MINT31) of the CACNA1G CpG island are hypermethylated in a wide variety of cancers. For example, Toyota et al., illustrates hypermethylation of regions 1 and 2 of CACNA1G of cancer cell lines from colon, lung, prostate, breast, brain, and hematopoietic neoplasms (*Cancer Research* 59:4535, at Fig. 2 (1999)) (Exhibit B). As indicated above, Ogi et al., cited in the office action, establishes that regions 1 and 2 (MINT31) of the CACNA1G CpG island are hypermethylated in oral squamous cell carcinoma. Furthermore, the Office Action acknowledges regarding Toyota et al., that the presence of hypermethylation of CACNA1G in some AML patients is commensurate in scope with the claims (Office Action at page 10) (*Blood*, 97:2823 (2001)). In addition, Chan, A.O., et al., (*Amer. Journ. Path.*, 160:529 (2002)(see e.g., Abstract)) (Exhibit C), and Rashid, A., et al., (*Amer. Journ. Path.*, 159:1129 (2001)) (Exhibit D), report that methylation of MINT31 is a common feature of the CpG island methylator phenotype (CIMP) of colorectal carcinomas and adenomas. Furthermore, Ueki, et al. report that CACNA1G is methylated in some patients with pancreatic adenocarcinoma. (*Canc. Res.*, 60:1835 (2000)) (Exhibit E). Finally, Strathdee et al report that MINT31 is frequently methylated in primary ovarian carcinomas (*Amer. Journ. Path.*, 158:1121 (See e.g., Table 1)) (Exhibit F).

Finally, the Office Action alleges that since CACNA1G is hypermethylated in a benign condition, comparing hypermethylation will not be indicative of cancer. It is not necessary to enable the pending claims, that CACNA1G only be hypermethylated in cancer. The pending claims recite a method for detecting a cancer or colorectal adenoma. As will be understood by a skilled artisan, routine methods, such as histology of biopsied cells, can be used if necessary, to further distinguish a cancer cell from a benign cell such as a colorectal adenoma cell that is hypermethylated at CACNA1G. Therefore, the fact that CACNA1G is hypermethylated in

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certain benign disorders as well as cancers, does not preclude its utility in detecting cancer or colorectal adenoma.

It is noteworthy that dependent claims 37-39 are directed at specific cancers disclosed in the specification as involving hypermethylation of CACNA1G, and claim 40 is specifically directed at colorectal adenoma. Therefore, these claims are even more clearly enabled by the disclosure as filed.

In summary, the claimed inventions of the pending claims are enabled by the disclosure as filed. Therefore, Applicant respectfully request removal of the rejection of claims 10, and 13-24 under 35 U.S.C. § 112, first paragraph.

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In view of the amendments and the above remarks, it is submitted that the application is in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: March 13, 2003

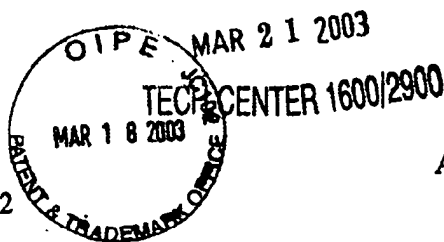


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Enclosures: Exhibits A-F

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Exhibit A - Page 1

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**EXHIBIT A: CLAIMS WITH MARKINGS TO SHOW CHANGES MADE**

**In the Claims**

Please cancel claims 1-10, 16-21, 25-32, and 34, without prejudice.

Please amend the claims as follows:

22. (Amended) The method of claim [10] 33, wherein the nucleic acid-containing specimen comprises a tissue selected from the group consisting of brain, colon, urogenital, lung, renal, prostate, pancreas, liver, esophagus, stomach, hematopoietic, breast, thymus, testis, ovarian, and uterine.

23. (Amended) The method of claim [10] 33, wherein the nucleic acid-containing specimen is selected from the group consisting of serum, urine, saliva, blood, cerebrospinal fluid, pleural fluid, ascites fluid, sputum, stool, and biopsy sample.

33. (Amended) A method for detecting a [cellular proliferative disorder associated with hypermethylation of CACNA1G] colorectal adenoma or a cancer other than a glioma, the method comprising contacting a nucleic acid-containing specimen from a subject with an agent that provides a determination of the methylation state of one or both of a first region and a second region of a CACNA1G CpG island [comprising any of SEQ ID NO:35-42], wherein hypermethylation of one or both of the first region or the second region of the CACNA1G CpG island is indicative of the presence of the [cellular proliferative disorder] colorectal adenoma or the cancer other than a glioma, thereby detecting the colorectal adenoma or a cancer other than a glioma.



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36. (Amended) The method of claim 35, wherein the primer pair is selected from SEQ ID NO:33 and 34; or SEQ ID NO: 35 and 36[; SEQ ID NO:37 and 38; SEQ ID NO:39 and 40; SEQ ID NO:41 and 42; SEQ ID NO: 43 and 44; SEQ ID NO: 45 and 46; SEQ ID NO:47 and 48; and SEQ ID NO:49 and 50].

37. (Amended) The method of claim 33, wherein the method detects [cellular proliferative disorder is] colorectal cancer, colorectal adenoma, gastric cancer, lung cancer, breast cancer, hematopoietic tumors, prostate cancer, or acute myeloid leukemia (AML).

38. (Amended) The method of claim 33, wherein the method detects [cellular proliferative disorder is astrocytoma, glioblastoma,] medulloblastoma, lung cancer, renal cancer, endometrial cancer or neuroblastoma.